ABSTRACT

Aims

To identify pre-treatment risk factors for the development of Palmar Plantar Erythrodysesthesia in participants receiving capecitabine monotherapy. Specifically the hypothesis that avoidance of activities that cause friction and pressure cause Palmar Plantar Erythrodysesthesia was tested.

Background

Previous literature showed contradictory evidence on the subject of predictors of chemotherapy-induced Palmar Plantar Erythrodysesthesia. There is a lack of empirical evidence to support the theory that Palmar Plantar Erythrodysesthesia is caused by damage to the microcapillaries due to everyday activities that cause friction or pressure to the hands or feet.

Design

Prospective epidemiological study of risk factors

Methods

Prospective data collection. All patients prior to commencing capecitabine monotherapy between 11th June 2009 and 31st December 2010, were offered recruitment into the study and followed for 6 cycles of treatment (n = 174). Data were collected during semi-structured interviews, from participants' diaries, physical examination of the hands and feet and review of notes. Data relating to activities that cause friction, pressure or heat were collected.

Data were analysed using bivariate (chi-square and independent groups Student's *t*) tests where each independent variable was analysed against Palmar Plantar Erythrodysesthesia.

Results

The only variables that were associated with an increased risk of Palmar Plantar Erythrodysesthesia were a tendency to have warm hands and pre-existing inflammatory disease.

Conclusions

This study gives no support for the hypothesis that avoidance of activities that cause friction and pressure cause Palmar Plantar Erythrodysesthesia.

KEYWORDS

Nursing, Cancer, Epidemiology, Quantitative Approaches, Palmar Plantar Erythrodysesthesia

SUMMARY STATEMENT

Why is this research or review needed?

- The risk factors for Palmar Plantar Erythrodysesthesia (PPE) are not known.
- PPE is a serious problem for patients receiving some chemotherapies.

What are the key findings?

- PPE is related to having hot hands.
- PPE is not related to activities that cause friction or pressure.

How should the findings be used to influence policy/practice/research/education?

- Patients probably do not benefit from avoiding activities that cause friction or pressure on the hands.
- Further research is needed to discover the causes of PPE.

INTRODUCTION

PPE is a reddening, swelling, numbness and desquamation of the palms of the hands or soles of the feet. It is a common side effect of chemotherapy. There are various grading systems, the one used here was according to the capecitabine clinical trial criteria (Blum et al. 1999) which grades PPE from 1 (least serious) to 3 (most serious). Capecitabine is an anti-neoplastic agent. It is a fluoropyrimidine carbamate and interferes with RNA processing and protein synthesis. It is converted to 5-fluorouracil (5-FU) initially in the liver with the final conversion by the enzymes cytidine deaminase and thymidine phosphorylase. 5-FU is an antimetabolite and acts as a false pyrimidine base (uracil), interfering with the synthesis of DNA by blocking the action of the enzyme thymidylate synthetase.

Background

Surprisingly unlike other toxicities, PPE had a higher incidence in patients with a good performance status (Chiara et al. 1997, Abushullaih et al. 2002). Age and gender have been suggested as risk factors for PPE, with some evidence that older, female patients have an increased risk of PPE (Meta-Analysis Group in Cancer 1998, Schellens et al. 2005, Chabner and Longo 2006), while others found no significant difference in age and gender (Comandone et al. 1993, Chiara et al. 1997, Abushullaih et al. 2002, Feliu et al. 2005, Sun et al. 2009). An increased risk of PPE has been reported in older patients and females receiving 5-FU(Meta-Analysis Group in Cancer 1998), and may be due to a lower capacity to clear 5-FU in women (Milano et al. 1992), but not in association with capecitabine (Abushullaih et al. 2002, Cassidy et al. 2002). A higher incidence of PPE has been seen in Japanese(Hyodo et al. 2006) and Korean patients(Yun et al. 2010), but with a lower incidence in grade 3 PPE which was also seen in Asian patients compared to other ethnic groups(Haller et al. 2008, Lee et al. 2008). Weight loss prior to a diagnosis of cancer was linked to an increased in cidence of severe PPE compared to those who had not lost weight. This is thought to be due to altered response to chemotherapy in patients with weight loss, since even 5% weight loss can alter

measurable physiological values such as immune response (Andreyev et al. 1998). Alcohol abuse has been associated with the development of PPE in patients receiving 5-FU or capecitabine with a suggestion that this group of patients should be prescribed pyridoxine from the start of treatment to reduce the severity of PPE (Vukelja et al. 1989).

Other patient-related factors linked to the development of PPE include; a pre-existing peripheral vascular disease, compromised peripheral nervous system - e.g. carpal tunnel syndrome(Zimmerman et al. 1995), peripheral neuropathy from previous chemotherapy (Palaia et al. 2006), diabetes(Narasimhan et al. 2004, Wilkes et al. 2005), dermatological disorders and previous irradiation therapy (Hood and Reeck 2006). Previous exposure to chemotherapy especially if the patient experienced toxicities such as mucositis, diarrhoea (Heo et al. 2004, Wagstaff et al. 2003) and neutropenia (Jansman et al. 2000) have been linked to the development of PPE. Whether these factors are statistically significant is unclear in some of the literature and are mostly based on case reports, and small scale studies and would require validation in larger studies.

Since PPE may result from increased vascularity, pressure and temperature(Arias et al. 1997) in the hands and feet, patient risk factors may include strenuous physical activity (Lassere and Hoff 2004), trauma and friction caused by normal activities such as walking or grasping objects, and long-term alcohol intake(Lassere and Hoff 2004).

Some studies, predominantly with patients receiving pegylated liposomal doxorubicin, have suggested that active cooling reduces the risk of developing PPE(Zimmerman et al. 1994, Mangili et al. 2008). Others have found the opposite with an increased incidence of PPE in those who used active cooling measures(Tanyi et al. 2009).

A previous retrospective analysis, undertaken by the first author, of patients who had received oxaliplatin and infusional 5-FU or capecitabine containing regimes between April 2008 and March 2009 showed the incidence of PPE was higher in those who received capecitabine monotherapy 50.3% (n=151) than in those receiving either other capecitabine containing regimes (22.9%, n=96) or infusional 5FU (7.6%, n=145). Thus the current study focussed on capecitabine monotherapy.

THE STUDY

Aims

To identify pre-treatment risk factors for the development of PPE in participants receiving capecitabine monotherapy. Specifically the hypothesis that avoidance of activities that cause friction and pressure cause Palmar Plantar Erythrodysesthesia was tested.

Design

Prospective epidemiological study of risk factors.

Sample/Participants

The sample was drawn from patients commencing capecitabine monotherapy from June 2009 to December 2010 from a general hospital in the East Midlands of England.

The only inclusion criterion was that the patient commenced capecitabine monotherapy in the study period. Exclusion criteria included those participants who did not wish to participate and those who were unable to speak English where an interpreter was not available. Four patients declined but there were no patients excluded because of language difficulties. The reason for declining was that participants felt they had too much going on in their lives at present without an additional meeting with another health care professional.

Most (70.2%) of participants were being treated for colorectal cancer, the next most common was breast cancer (8.4%). All participants received more than one cycle of chemotherapy, unless the treatment was stopped following the first cycle due to severe toxicities including PPE (only one participant).

Data collection

Variables that are found in the literature to be thought to be related to PPE were collected and in particular actions that may cause friction to the hands or feet. Participants were encouraged to complete a symptom diary. Completion varied ranging from those that kept no records to those who kept very detailed accounts of what occurred between cycles. Participants were questioned about activities such as regular walking, dancing, gardening, DIY, playing musical instruments, sewing, knitting and rubbing hands with moisturising cream regularly. Data were thus collected during semi-structured interviews, from participant's diaries and physical examination of the hands and feet and notes review.

Apart from age, body surface area and creatinine, which were continuous data, all variables were categorical and most binary. These are shown in Table 1. N.B. many of these variables were originally collected in finer granularity (e.g. ethnic group) but due to small numbers have been collapsed into two or a few categories.

Ethical considerations

Ethical approval was gained from a university ethics committee and from an NHS local ethics committee.

Data analysis

Data were analysed independently using bivariate (chi-square and independent groups Student's *t*) tests where each independent variable was analysed against PPE. The variables which achieved a $p<0.1$ were entered into a binary logistic regression model.

Validity and reliability/Rigour

Power of 80% with an effect size of 0.3 (medium) and the significance level of 0.05 were used in this study and sample size estimated using G* Power version 3.1 priori analysis program(Faul et al. 2007). A sample size of 108 participants was determined for a bivariate analysis. However all variables with a $p<0.1$ were considered candidate variables for logistic regression.

RESULTS

Baseline

A total of 174 participants of whom 44.8% were male were included in the analysis. There was no significant difference between men and women with respect to PPE. The sample characteristics are presented in table 2.

Toxicity

Fatigue and diarrhoea were the most common adverse side effects. The incidence of toxicity is listed in table 3, the figures reflecting the development of multiple toxicities in many participants. The incidence of the toxicities was similar except for the development of a rash which was infrequent. PPE developed in 93 participants (53.4%) with 74 (42.5%) developing PPE during the first three cycles of their treatment.

Univariate analysis

The p values for variables are shown in table 4. Only three variables were significant at $p<0.1$ – cool hands, inflammatory disease and diabetes.

Logistic regression

The omnibus tests of model coefficient revealed a chi-square statistic of 10.3 (df, 3) p =0.016 indicating that the model performs well compared to the baseline model before the variables were added. The Hosmer-Lemeshow statistic was applied to the data revealing a chi-square statistic of 1.12 (df, 4) p = .89 which indicates that the observed numbers who develop PPE are not significantly different from those expected by the model and that the overall fit is good. The Nagelkerke R^2 (0.089) value shows about 9% of the variation in the outcome variable (PPE) is explained by the logistic model and the percentage correctly predicted in this model was 58.7%

The outcome of the logistic regression analysis produced a model containing 2 predictors pre existing inflammatory conditions and cool hands, see table 5.

DISCUSSION

This research explored numerous potential risk factors of PPE. The findings will add to the current evidence of biographical data, performance status(Oken et al. 1982), co-morbidities and renal function as risk factors of PPE. Since this is the first time that individual activity related factors have been studied, this is the unique contribution made by this research. The findings raise questions about the current advice given to patients receiving capecitabine to avoid activities that cause friction or exposure to high temperatures. Whilst it is acknowledged that the findings need validating by further research they have implications for nursing practice. The main findings are that having cool hands is protective and having pre-existing inflammatory disease increases risk of PPE. However the prediction of PPE with the logistic regression remains very low with a small amount of variance accounted for by the significant variables.

The advice to avoid exposure to heat and keeping the hands cool may be considered reasonable as cool hands were a protective variable, though whether having cool hands implies making hands cool is beneficial is a moot point. All other activities were not confirmed statistically as having any association with the development of PPE. Whilst these findings will need validating in further large prospective studies, they do suggest that avoidance of some activities is unnecessary unless PPE develops.

Until such a time that the evidence base for avoiding friction or pressure causing activities is established, the focus should be on careful monitoring, questioning and assessment. There is evidence that early onset of grade 1 PPE results in an increased risk of developing more severe PPE in subsequent cycles. Careful questioning of patients to identify PPE developing between cycles which has resolved, may identify those who would benefit from early dose reduction to avoid delays in treatment due to severe PPE. This is particularly important in light of the emerging evidence that PPE may be a marker of efficacy of treatment. This would indicate that those who develop PPE and the ones most likely to benefit from continuing treatment.

Another recommendation would be to ensure men receiving agents that are known to cause PPE are educated about the possibility of penile and scrotal involvement, giving them permission to report this, which, if identified early, may reduce its severity.

The evidence for strategies to prevent or manage PPE once it develops is weak. The only agent that has been subjected to randomised controlled trials is pyridoxine demonstrating that the findings cannot support its use to avoid or manage PPE. The use of emollients has not been subjected to rigorous testing. However, since one of the early symptoms of PPE is dryness and flaking, the use of emollients would seem logical. Since it a safe and uncontroversial substance its use can be recommended without ill effects.

Limitations

Stratification may have produced different results. However, this would have required a much larger sample from which to randomly select subjects from each group.

Data collection restricted to one geographical site lacks generalisability. Similarly data collection restricted to a single chemotherapy agent cannot be generalised to other agents. Although, if we accept the notion that there may be different pathophysiological mechanisms and risk factors for PPE between different agents, this may in fact be the study's strength. Large scale studies focusing on each different drug would enable comparison of data to test commonality or variability.

CONCLUSION

Current practice with patients commencing capecitabine involves advising them to avoid activities that cause friction, pressure or high temperature. The evidence base for this is based on consensus and case reports. There are no previous large studies to validate this advice. This study is the first that has tested any association between activities that cause

friction, pressure or high temperature and PPE and the data reported here to not support this advice.

The significant variables found, despite considering all those located in the literature, remain poor predictors of PPE. We conclude we still do not know what causes PPE but it is unlikely to be activities that cause friction.

REFERENCES

Abushullaih, S., Saad, E.D., Munsell, M. & Hoff, P.M. (2002) Incidence and severity of hand-foot syndrome in colorectal cancer patients treated with capecitabine: a single-institution experience. *Cancer Invest,* **20**(1), 3-10.

Andreyev, H.J., Norman, A.R., Oates, J. & Cunningham, D. (1998) Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer,* **34**(4), 503-9.

Arias, F., Valcayo, A., Illarramendi, J.J., Martinez, E., Duenas, M. & Dominguez, M.A. (1997) Acral erythema and intrahepatic 5-fluorouracil infusion *Journal of the European Academy of Dermatology and Venereology,* **8**, 259-260.

Blum, J.L., Jones, S.E., Buzdar, A.U., LoRusso, P.M., Kuter, I., Vogel, C., Osterwalder, B., Burger, H.U., Brown, C.S. & Griffin, T. (1999) Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *Journal of Clinical Oncology,* **17**, 485-493.

Cassidy, J., Twelves, C., Van Cutsem, E., Hoff, P., Bajetta, E., Boyer, M., Bugat, R., Burger, U., Garin, A., Graeven, U., McKendric, J., Maroun, J., Marshall, J., Osterwalder, B., Perez-Manga, G., Rosso, R., Rougier, P., Schilsky, R.L. & Capecitabine Colorectal Cancer Study, G. (2002) First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. *Ann Oncol,* **13**(4), 566-75.

Chabner, B.A. & Longo, D.L. (2006) *Cancer Chemotherapy and Biotherapy. Principles and Practices 4th Ed* Lippincott Williams and Wilkins, Philadelphia.

Chiara, S., Nobile, M.T., Barzacchi, C., Sanguineti, O., Vincenti, M., Di Somma, C., Meszaros, P. & Rosso, R. (1997) Hand-foot syndrome induced by high-dose, short-term, continuous 5-fluorouracil infusion. *Eur J Cancer,* **33**(6), 967-9.

Comandone, A., Bretti, S., La Grotta, G., Manzoni, S., Bonardi, G., Berardo, R. & Bumma, C. (1993) Palmar-plantar erythrodysestasia syndrome associated with 5-fluorouracil treatment. *Anticancer Res,* **13**(5C), 1781-3.

Faul, F., Erdfelder, E., Lang, A.G. & Buchner, A. (2007) G*Power 3: A flexible statistical power analysis program for the social, behavioural, and biomedical sciences. *Behaviour Research Methods,* **39**(2), 175-191

Feliu, J., Escudero, P., Llosa, F., Bolanos, M., Vicent, J.M., Yubero, A., Sanz-Lacalle, J.J., Lopez, R., Lopez-Gomez, L., Casado, E., Gomez-Reina, M.J. & Gonzalez-Baron, M. (2005) Capecitabine as first-line treatment for patients older than 70 years with metastatic colorectal cancer: an oncopaz cooperative group study. *J Clin Oncol,* **23**(13), 3104-11.

Haller, D.G., Cassidy, J., Clarke, S.J., Cunningham, D., Van Cutsem, E., Hoff, P.M., Rothenberg, M.L., Saltz, L.B., Schmoll, H.J., Allegra, C., Bertino, J.R., Douillard, J.Y., Gustavsson, B.G., Milano, G., O'Connell, M., Rustum, Y., Tabernero, J., Gilberg, F., Sirzen, F. & Twelves, C. (2008) Potential regional differences for the tolerability profiles of fluoropyrimidines. *J Clin Oncol,* **26**(13), 2118-23.

Heo, Y.S., Chang, H.M., Kim, T.W., Ryu, M.H., Ahn, J.H., Kim, S.B., Lee, J.S., Kim, W.K., Cho, H.K. & Kang, Y.K. (2004) Hand-foot syndrome in patients treated with capecitabine-containing combination chemotherapy. *J Clin Pharmacol,* **44**(10), 1166-72.

Hood, A.F. & Reeck, M.C. (2006) Dermatologic toxicity. In *The Chemotherapy Source Book*(Perry, M. C. ed. Lippincott Williams & Wilkins, Philadelphia.

Hyodo, I., Shirao, K., Doi, T., Hatake, K., Arai, Y., Yamaguchi, K., Tamura, T., Takemiya, S., Takiuchi, H., Nakagawa, K. & Mishima, H. (2006) A phase II Study of the global dose and schedule of capecitabine in Japanese patients with metastatic colorectal cancer. *Jpn J Clin Oncol,* **36**(7), 410-7.

Jansman, F.G., Sleijfer, D.T., Coenen, J.L., De Graaf, J.C. & Brouwers, J.R. (2000) Risk factors determining chemotherapeutic toxicity in patients with advanced colorectal cancer. *Drug Saf,* **23**(4), 255-78.

Lassere, Y. & Hoff, P. (2004) Management of hand-foot syndrome in patients treated with capecitabine (Xeloda). *Eur J Oncol Nurs,* **8 Suppl 1**, S31-40.

Lee, J.L., Kang, Y.K., Kang, H.J., Lee, K.H., Zang, D.Y., Ryoo, B.Y., Kim, J.G., Park, S.R., Kang, W.K., Shin, D.B., Ryu, M.H., Chang, H.M., Kim, T.W., Baek, J.H. & Min, Y.J. (2008) A randomised multicentre phase II trial of capecitabine vs S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. *Br J Cancer,* **99**(4), 584-90.

Mangili, G., Petrone, M., Gentile, C., De Marzi, P., Vigano, R. & Rabaiotti, E. (2008) Prevention strategies in palmar-plantar erythrodysesthesia onset: the role of regional cooling. *Gynecol Oncol,* **108**(2), 332-5.

Meta-Analysis Group in Cancer (1998) Toxicity of fluorouracil in patients with advanced colorectal cancer: Effect of administration schedule and prognostic factors *Journal of Clinical Oncology,* **16**(11), 3537-354.

Milano, G., Etienne, M.C., Cassuto-Viguier, E., Thyss, A., Santini, J., Frenay, M., Renee, N., Schneider, M. & Demard, F. (1992) Influence of sex and age on fluorouracil clearance. *J Clin Oncol,* **10**(7), 1171-5.

Narasimhan, P., Narasimhan, S., Hitti, I.F. & Rachita, M. (2004) Serious hand-and-foot syndrome in black patients treated with capecitabine: report of 3 cases and review of the literature. *Cutis,* **73**(2), 101-6.

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T. & Carbone, P.P. (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol,* **5**(6), 649-55.

Palaia, I., Angioli, R., Bellati, F., Basile, S., Rabitti, C. & Panici, P.B. (2006) Distal phalange necrosis: a severe manifestation of palmar plantar erythrodysesthesia. *Am J Obstet Gynecol,* **195**(4), e1-2.

Schellens, J.H.M., McLeod, H.L. & Newell, D.R.e. (2005) *Cancer Clinical Pharmacology* Oxford University Press, Oxford.

Sun, J.F., Wu, R.R., Norris, C., Noone, A.M., Amankwa-Sakyi, M., Slack, R. & Marshall, J.L. (2009) Safety of chronic low-dose capecitabine as maintenance therapy in gastrointestinal cancers. *Gastrointest Cancer Res,* **3**(4), 134-40.

Tanyi, J.L., Smith, J.A., Ramos, L., Parker, C.L., Munsell, M.F. & Wolf, J.K. (2009) Predisposing risk factors for palmar-plantar erythrodysesthesia when using liposomal doxorubicin to treat recurrent ovarian cancer. *Gynecol Oncol,* **114**(2), 219-24.

Vukelja, S.J., Lombardo, F.A., James, W.D. & Weiss, R.B. (1989) Pyridoxine for the palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med,* **111**(8), 688-9.

Wagstaff, A.J., Ibbotson, T. & Goa, K.L. (2003) Capecitabine: a review of its pharmacology and therapeutic efficacy in the management of advanced breast cancer. *Drugs,* **63**(2), 217-36.

Wilkes, L., Cert, R. & Beale, B. (2005) Role conflict: appropriateness of a nurse researcher's actions in the clinical field. *Nurse Res,* **12**(4), 57-70.

Yun, J.A., Kim, H.C., Son, H.S., Kim, H.R., Yun, H.R., Cho, Y.B., Yun, S.H., Lee, W.Y. & Chun, H.K. (2010) Oncologic outcome after cessation or dose reduction of capecitabine in patients with colon cancer. *J Korean Soc Coloproctol,* **26**(4), 287-92.

Zimmerman, G.C., Keeling, J.H., Burris, H.A., Cook, G., Irvin, R., Kuhn, J., McCollough, M.L. & Von Hoff, D.D. (1995) Acute cutaneous reactions to docetaxel, a new chemotherapeutic agent. *Arch Dermatol,* **131**(2), 202-6.

Zimmerman, G.C., Keeling, J.H., Lowry, M., Medina, J., Von Hoff, D.D. & Burris, H.A. (1994) Prevention of docetaxel-induced erythrodysesthesia with local hypothermia. *J Natl Cancer Inst,* **86**(7), 557-8.

Table 1 Variables

Variable	Values
Age	Continuous
Aim of treatment	Adjuvant , Neoadjuvant , Palliative
Albumin	Low, normal (35-55g/L) or high
Alcohol	No/yes
Alkaline phosphatase	Low, normal (40-130 iu/L) or high
Alanine Aminotransferase	Low, normal (2-53 iu/L) or high
Bilirubin	Low, normal (3-17 umol/L) or high
Body mass index	Underweight < 18.5; Normal weight 18.5-24.9; Overweight 25-29.9; Obesity ≥ 30
Body surface area	Continuous
Normal Cool feet	No/yes
Cool hands	No/yes
Creatinine clearance	<50; 50-80;>80
Creatinine	Continuous
Diabetes	No/yes
Dry skin	No/yes
Employment	Working or not
Ethnicity	White/not White
Regular hand cream	No/yes
Hobbies with friction	Any of gardening, DIY/using tools, Walking, Dancing, Sewing/knitting or Other (especially using hands & feet) or not
Hot water	No/yes
Inflammatory diseases	No/yes
Marital status	In a relationship or not
Metastatic spread	No/yes
Other capecitabine-	No/yes

induced toxicities	
Performance status	0. Fully active, able to carry on all pre-disease performance without restriction 1. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work 2. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours 3. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours 4. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair 5. Dead
Peripheral neuropathy	No/yes
PPE with previous chemotherapy	No/yes
Previous cancer diagnosis	No/yes
Previous radiotherapy	No/yes
Peripheral vascular disease	No/yes
Recent weight loss	No/yes
Skin type	Dry or moist/sensitive
Skin complaint	No/yes
Smoker	No/yes
Start season	Summer or winter
Recent sunburn	No/yes
Sweaty feet	No/yes
Sweaty hands	No/yes
Tumour type	Breast, colorectal or other

Table 2 Patient characteristics

Age mean	64.1
SD	10.8
Gender (Male)	44.8%
Ethnicity	
White	94.2%
Non-white	5.8%
Marital status	
In a relationship	76.4%
Not in a relationship	23.6%
Employment	
Working	39.8%
Not working	60.2%
Tumour site	
Colorectal	63.8%
Breast	25.9%
Other[c]	10.3%
Metastatic spread	45.1%
PPE with previous chemo	8.0%
Season start	
Summer	48.3%
Winter	51.7%

Table 3: Toxicity

	No PPE	PPE	P value (chi square)
Diarrhoea	46.9%	49.5%	0.427
Mucositis	21.0%	40.9%	0.005
N & V	37.0%	47.3%	0.171
Rash	3.7%	6.5%	0.414
Fatigue	43.2%	46.2%	0.689

Table 4: Chi-square test for association between variables and development of PPE before cycle 4

Variable	*P*value
Age	0.141
Aim of treatment	0.951
Albumin	0.499
Alcohol	0.638
Alkaline phosphatase	0.222
Alkaline phosphatase	0.651
Biirubin	0.839
Body mass index	0.201
Body surface area	0.538
Cool feet	0.372
Cool hands	0.041
Creatinine clearance	0.709
Creatinine	0.131
Diabetes	0.061
Dry skin	0.442
Ethnicity	0.238
Gender	0.718
Hand cream	0.100
Hobbies	0.975
Hot water	0.558
Inflammatory conditions	0.040
Jobs	0.907
Marital status	0.875
Met astatic spread	0.674
Performance status	0.355

Peripheral neuropathy	0.242
PPE with previous chemo	0.190
Previous cancer diagnosis	0.230
Previous deep X Ray treatment	0.360
Peripheral vascular disease	0.301
Recent weight loss	0.981
Skin complaints	0.872
Skin type	0.622
Smoker	0.742
Start season	0.824
Sunburn	0.355
Sweaty feet	0.338
Sweaty hands	0.173
Tumour site	0.400

Table 5: Logistic regression output predictors of PPE

	Odds ratio	Lower 95% CI	Upper 95% CI	Sig.
Diabetes	0.448	0.156	1.286	0.136
Inflammatory conditions	2.114	1.016	4.398	0.045
Cool hands	0.496	0.251	0.980	0.044
Constant	0.951			0.840